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Does Aging or Endothelial Dysfunction Pose a Threat to Military Crewmembers?

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SUMMARY

Aging is a physiologic process associated with an increase of health conditions limiting somewhat an aviator's performance abilities generally. What is more, vascular aging is closely linked with an increase in cardiovascular morbidity and mortality. This may be related to cellular changes due to an increased oxidative stress or/and to an impaired release of vasoactive mediators by endothelium cells. Endothelium-dependent relaxation decreases with aging. Consequent cardiovascular changes and damages with or without the presence of other risk factors and bad life style habits may speed up that process. This may lead to clinical manifestation of the disease, grounding, treatment and even to a permanent disqualification from flying duty not surprisingly within the third and fourth decade. Besides aging, which is an independent risk factor per se, there are new scientific discoveries which have refined our understanding of the endothelium dysfunction process complexity. Additionally, it has been proven that some medicaments like HMG-CoA reductase inhibitors, ACE inhibitors and Ca antagonists, particularly those with a long duration of action, improve endothelium function of the coronary circulation in patients with atherosclerosis or hypertension along with an appropriate physical activity, smoking cessation, glucose intake restriction etc. The content of this paper is focused on highlighting new aspects of aging, links between them, mechanisms of action and interaction. The whole process should be seen as a complex of mechanical, humoral, nutritious, metabolic, endocrine and exogenous factors interplay, having a deleterious impact on human health status, crewmembers including. The end-stage occurs more earlier than simply in the course of natural aging process. Better understanding of these facts was contrasted with

clinical findings among the group of Czech military aviators primarily treated for hypertension, as well as for hyperlipidemia and hyperuricemia over the past five years. We succeeded in good control of hypertension pharmacologically, but we failed with influencing of other discovered risk factors. No wonder, that prior to ending up this study, three aviators were disqualified for flying duty due to coronary artery disease (CAD) development. Based on comparison of known experimental facts, clinical trial outcomes and our findings, we have tried to formulate possible pathways for changing our minds and defined particular steps in order to reverse the unwanted trends reached so far in the management of cardiovascular diseases. These steps consist of non-pharmacological and pharmacological interventions in crewmembers. The answer to the question at the beginning will be more elucidated and sophisticated steps then formulated at the end of this paper.

INTRODUCTION

The health status worsens with aging and there is an increase in conditions limiting aviator's performance ability. The opposite state, marked as vitality of an individual, can be defined as a summation of all functional capacities of his important organs and homeostatic systems that are essential for his survival. Human functional capacity is supposed to decline with aging roughly linearly at about 1% per year after the age of 30 in male subjects despite the fact, that literature increasingly supports the argument, that declining trends in CAD mortality reflect changes in cardiac risk factors identification and modification (4). It has become apparent, that the policy of primary prevention should have been instituted in the aviators population more vigorously than it has been done so far (20). Relationship between

increasing cardiac risk and age have been shown in Framingham (5,7,10,14) as well as in other previous studies (24, 29). Although the death rate for CAD has been declining by approx. 2-3% per year for the past 15 years, it still remains an important cause of morbidity and death (10,24). When looking back at the categories of medical conditions which have most often been responsible for permanent disqualification of flying personnel, cardiovascular diseases as a category were found the commonest ones – precisely in 30% (29). The first and second place most frequent diseases were CAD and hypertension, each accounting for 10%, third and fourth position were placed by spinal disorders and diabetes mellitus. These illnesses were found predominantly in the over-40 years age category. In the lower age categories the prevalence was lower (29). Based on these references and on data obtained from current observational studies among USAF and Czech waived aviators for different chronic illnesses, hypertension was the most frequent cause for non and pharmacological interventions (26). It has been discovered an increase in metabolic disorders in both countries as well (25,26).

Since that time when risk factors for CAD have been recognized, many experimental and clinical studies have been conducted. The outcomes were contributive to better understanding of cardiovascular pathophysiology. (7,15,19). It is noteworthy, that for nitric oxide (NO) or endothelium-derived relaxing factor (EDRF) discovery a Nobel Price in the last year was awarded.

BIOLOGY OF ENDOTHELIUM

Endothelial cells as the inner lining of the vessels are strategically located between circulating blood, blood cells and vascular smooth muscles. In a person with the body weight of 70 kg, the endothelium covers an area of approx. 700 m² and weights about 1 to 1.5 kg. Its functional integrity is crucial for maintenance of blood flow and antithrombotic capacity due to control of essential functions like relaxation, vasoconstriction, thrombogenesis, fibrinolysis, platelet activation and inhibition. Thus, the endothelium contributes to blood pressure control, blood flow and vessel patency. Conversely, the impaired endothelial function contributes substantially to cardiovascular disorders such as atherosclerosis, hypertension, CAD, heart failure,

etc., with their sequelae for the end-organs functioning (1,2,3,5,7,15, 23,24).

PHYSIOLOGY OF THE ENDOTHELIUM

Endothelium-derived Relaxing Factor

Stimulation of intact endothelial cells by various substances like neurotransmitters, hormones, agents derived from platelets and coagulation system causes release of a substance marked NO or EDRF which induces relaxation of underlying vascular smooth muscles. What is more, shear stress (forces exerting on the vessel wall during the cardiac cycles) generated by circulating blood flow induce endothelium-dependent vasodilatation. This is an important adaptive response of the vasculature during the physical activity as well. NO production is regulated with an enzyme NO synthase released constitutively as well as by shear stress and estrogens. There is a clear evidence, that vasculature is in a constant state of vasodilation due to continuous basal release of NO by the endothelium. Furthermore, endothelial cells release prostacyclin (PGI₂) in response to shear stress and hypoxia which like NO synergistically inhibits platelet aggregation.

Endothelium-derived Contraction Factors

After NO existence has been discovered, it became clear, that it must exist a contracting factor as well. Endothelium-derived contracting factors involve group of endothelin-1,2,3 (ET-1,2,3) and a family of 21-amino acid peptide prostanoids like thromboxane A₂, prostaglandin H₂ and components of renin-angiotensin system (RAS) such as angiotensin II (AT II). Cardiovascular endothelial cells produce ET-1 exclusively. An important role in the transformation and expression of ET-1 plays an endothelium-converting enzyme (ECE). Release of ET-1 is stimulated by thrombin, transforming growth factor beta, interleukin-1, epinephrine, AT II and arginin-vasopressin. ET-1 causes vasodilation in lower concentration, but marked and sustained contraction at higher concentration. In the heart, it may eventually lead to ischemia, arrhythmias or even a sudden death. What is of interest, intramyocardial vessels are more sensitive to ET-1 effect than epicardial coronary arteries. ET-1 have inhibitory factors as well. To the main four substances pertain cGMP-dependent inhibitor, cAMP-dependent inhibitor, inhibitory

factor produced by smooth muscle cells and estrogens. Additionally, the endothelium regulates the activity of the RAS due to ACE expression on the endothelial cell membrane either. This substance is identical to kinase II, which inactivates bradykinin.

ENDOTHELIUM PATHOPHYSIOLOGY – ENDOTHELIAL DYSFUNCTION

Endothelium dysfunction can be defined as an imbalance of endothelium-derived relaxing and contracting factors. It may be the cause or consequence of vascular disease and is a hallmark of known cardiovascular risk factors (17). It is essential that endothelial dysfunction precedes structural vascular alterations indicating a protective role of the functionally intact endothelium. Normally, endothelium does not stimulate migration and proliferation of vascular smooth muscle cells. But with onset of endothelial dysfunction, platelets and monocytes adhere to the vessel wall and later on, the growth factors are released not only from these cells, but also from the endothelium.

Cardiovascular Risk Factors and Endothelial Dysfunction

Aging

Aging is now recognized as an important independent risk factor for cardiovascular diseases development. The effect of aging in humans on endothelium-dependent vasodilation of coronary arteries is characterized by significantly decreased coronary blood flow response to acetylcholine (ACh). Age-related decrease in the production or responsiveness to NO, increased response to/or production of vasoconstricting factors, or increased degradation of NO respectively, are typical findings which may lead to the mentioned effects. Moreover, there is a difference between genders in the loss of flow-mediated dilation. The decline in men used to begin toward the end of fourth decade, in women this process did not start until after the early fifties. Later on, approximately at around the age of 65, endothelial dysfunction is supposed to be found in all subjects.

Vascular aging seems to be caused either by impaired release of vasoactive mediators or by an increased oxidative stress. In most studies, endothelium-dependent relaxations decrease with aging, or an increase in coronary flow induced by

acetylcholine infusion lessens with age. Recent studies support the idea, that the decline in endothelium-dependent relaxation may be related to a decrease either in basal or stimulated release of NO and/or to reduced expression of the endothelial NO synthase gene. Although the plasma level of ET-1 increases with age, organs response to its release decreases, presumably due to receptors downregulation. Furthermore, functional ECE activity is heterogeneously affected with aging, which may lead to an increase in some, but not all arteries.

Hypercholesterolemia and Atherosclerosis

Hypercholesterolemia per se, i. e. without atherosclerotic vascular changes, inhibits endothelium-dependent relaxation, which is more extensive in more advanced atherosclerosis. What is more, hypercholesterolemia enhances the response to vasoconstriction agonists and attenuates endothelium-dependent relaxations in isolated vessels. Reduced activity of endothelium-dependent NO is an initiating factor in atherogenesis. The key role in that phenomenon plays LDL-cholesterol, particularly after a oxidation. The oxidized LDL-cholesterol impairs the activity of NO synthase enzyme. The consequence is, that both in hypercholesterolemia and atherosclerosis, biologically active NO is substantially reduced. It has been revealed, that endothelium-derived NO fosters the inhibition of several pathologic processes like monocyte adherence and chemotaxis, platelet adherence and aggregation and finally vascular smooth muscle proliferation. Fortunately, the endothelial dysfunction is a reversible process, which can be positively influenced by administration of NO precursor L-arginine in hypercholesterolemic individuals (1). Conversely, endothelin-1 is activated in atherosclerotic vascular disease, as well as by hyperlipidemia. As it has been stated, likely the most stimulus for the increased endothelin-1 production is LDL-cholesterol level, which increases endothelin gene expression and release. Additionally, vascular smooth muscle cells migrating into the intima during the atherosclerotic process produce endothelin-leither.

Hypertension

Hypertension is another condition when endothelial dysfunction may contribute to an increase in peripheral resistance, particularly in

small arteries, or to vascular complications of the disease in medium and large-sized conduit arteries. In most models of hypertension, this illness is associated with reduced endothelium-dependent relaxation. Endothelial dysfunction seems to be more the consequence rather than a cause of hypertension. The endothelial dysfunction in individuals with essential hypertension appears to be due to a defect in the NO synthase pathway, that is unfortunately not reversible by NO precursor L-arginin administration. Similarly the salt-induced hypertension is associated with markedly impaired endothelial NO synthase activity. A defect in the endothelium-derived NO system, possibly decreased synthesis and/or release of NO by endothelial cells, is now known to cause the abnormal response to Ach in hypertensive vessels and thus partially contributes to increased vascular resistance typical for hypertension. There have been four mechanisms responsible for it in consideration, but none of these mechanisms have been proven so far definitely (1).

Diabetes mellitus

In case of *diabetes mellitus* it has been proven, that an elevated level of glucose cause endothelial dysfunction. Mechanism hidden behind that phenomenon may involve an increased synthesis of endothelin-1 and/or impairment in NO expression pathway. Reduced production of NO does not seem to be the cause of the impaired relaxation. A particular role pertains rather to prostaglandin having a vasoconstricting effect in response to higher glucose level, which in reality overcomes the normal vasodilating effect of NO released by endothelium. Otherwise, there is a consensus, that elevated glucose plasma levels contribute to higher oxidative stress, which may lead to natural antioxidant power perturbation, i.e. may bring about a lack of defense.

Sedentary Lifestyle

A lack of exercise generally is considered as a risk factor for atherogenesis, independent on its negative effects e.g. on body weight, blood pressure and lipid status. It has been discovered, that the lack of an adequate physical activity may be associated with reduced expression of NO synthase and thereby with decreased synthesis of NO.

Estrogen deficiency

It has been proven that estrogen replacement therapy is associated with a decreased risk of cardiovascular morbidity and mortality in postmenopausal women (1). Accordingly, the male gender is considered as an independent risk factor for CAD. On one hand, estrogen modulates NO synthase activity and thus the production of NO. On the other hand, estrogen deficiency is associated with endothelial dysfunction development and increased levels of circulating endothelin-1. These clinical findings show a possible and reasonable pathway how to change our approach to the prevention from consecutive endothelial dysfunction alterations.

Smoking

The main effect of cigarettes smoking can be summarized as vasoconstriction, platelet aggregation and monocyte adhesion, which contribute undoubtedly to increased risk of atherosclerosis and other forms of cardiovascular diseases. It is supposed to be a higher turnover and desquamation of the endothelium cells with expected sequelae (1).

Stress

Stress environment, particularly in aviation, can not be omitted. It has been recognized as an important part of this profession and deleterious condition even for cardiovascular disease development as well (9,12,20). Any aviator more or less, must face with it, especially during operational missions, overseas operations etc. The simple clinical sign of activated sympathetic system is the tachycardia. It has been confirmed in current studies (13,30) that the increased heart rate (HR) is an independent risk factor or even predictor for coronary mortality(11). It can be currently summarized: firstly, tachycardia pertains to the reliable markers of increased sympathetic activity. Secondly, there is a statistically significant correlation between tachycardia and later hypertension development (12). Thirdly, tachycardia is a predictor of later CAD development. A typical response to acute or repeated stress stimulus is characterized by catecholamines release, which is regulated via hypothalamus-pituitary gland-peripheral organs pathway. Moreover, higher HR is associated with hyperglycemia and hypercholesterolemia as well

(11). It is well known, that s.c. borderline hypertension is linked with hyperdynamic circulation and is recognized as an important risk factor in some individuals. The imbalance between sympathetic and parasympathetic nerves is supposed to be a triggering mechanism. Moreover, the whole process is influenced negatively by smoking, alcohol intake, bad dietary regimens and finally with the individual's mood, e.g. anxiety. Sympathetic activation leads to the catecholamines excretion. The clinical response to catecholamine release leads to a remarkable increase in HR, cardiac output, blood pressure and platelet aggregation as well. Moreover, catecholamines speed up the vessel's wall aging process by hypertension development and tendency to thrombogenesis. Combination of higher catecholamine plasma levels and hyperinsulinemia contributes cumulatively to the vessel's wall damages, particularly endothelial cells and smooth muscle cells located in the media. The impact is progression of atherogenesis. Finally, catecholamines interact both with alpha and beta-receptors. Alpha-receptors activation leads to vasoconstriction with a reduction of blood flow to the organs.

The second phase of stress reaction can be characterized by a higher cortisol production. Consequently the extracellular volume, cortisol, as well as ACE excretion increases, the excretion of kinase and prostaglandines decreases. These changes cause at the end the increase in cardiac output and peripheral vessels resistance. Furthermore, with aging and associated higher responsiveness to cortisol, the duration of recovery phase becomes longer.

Endothelial Function and Oxidative Stress

The increased oxidative stress has been linked to a wide variety of degenerative processes and diseases such as atherosclerosis, stroke, ischemia and a wide variety of age-related disorders and the aging process. Sometimes it is difficult to demonstrate cause and effect relationships between these diseases and antioxidant state because oxidant damage is subtle, difficult to measure, which develops over the years. In order to survive in the "unfriendly" environment created by oxygen radicals, living organisms generate a variety of water- and lipid-soluble antioxidants. As antioxidant can be marked any substance, which delays the oxidation of the substrate. They

may work by preventing the generation of oxidizing species, by scavenging or by reducing free radicals. The inactivation of free radicals also known as "chain breaking" is particularly important in lipid structures that contain easily oxidizable compounds like LDL-cholesterol and unsaturated fatty acids. There is a battery of endogenously synthesized antioxidant enzymes such as superoxide dismutase enzyme (SOD), catalase, glutathione peroxidase, which intercept and inactivate these reactive species. Problems arise, when the amount of oxidative stress overwhelms the capacity of antioxidants. Both endothelial and vascular smooth muscle cells are capable of producing reactive oxygen species from variety of enzymatic sources. In disease state, e.g. hypertension, production of these reactive oxygen metabolites can increase substantially. Higher production of superoxide anion may lead to decreases in ambient levels of NO due to facile radical reaction more rapidly than the excretion of superoxide anion caused by SOD. This phenomenon alters endothelial regulation of vasomotion in different diseases. The major source of vascular superoxide ion and hydrogen peroxide is a membrane-bound, reduced nicotinamide-adenine-dinucleotide (NADH)-dependent oxidase. The activity of this enzyme is regulated by AT II and is elevated after a prolonged nitroglycerin administration as well. Alterations of vascular oxidant state caused by AT II may contribute to vascular pathology and provide a link between hypertension and atherosclerosis.

Vasculoprotective and Cardioprotective Mechanisms of ACE Inhibition: Balance between AT II and NO

The process of vascular remodeling – *the ability of vasculature to modify its geometry in accordance with conditions of its microenvironment* – represents an important pathophysiologic process common to vascular disorders. A growing body of evidence indicates, that locally generated vasoactive substances like AT II and NO are those determinants of the natural history of vascular diseases. AT II may also promote chronic hypertension by modulating the vascular redox state and promoting the catabolism of endothelium-derived NO. Thus, the ACE inhibition may have reasonably a profound effect on ventricular and vascular structure and

have particular efficacy in preventing the cardiovascular morbidity and mortality.

Role of Angiotensin II

Vascular remodeling involves a cascade of alterations. These alterations in vessel structure are now considered as essential determinants of vascular resistance and hypertension pathogenesis. There are several forms of remodeling, involving medial layer hypertrophy, decreased vessel and/or lumen diameter, expansion and/or alteration of the extracellular matrix and vessel rarefaction (microvessel occlusion). Final stages are then vascular hypertrophy and fibrosis within the structure of conduit and microcirculation, resulting from vascular remodeling. The balance between mechanisms governing vascular tone, i. e., an interplay between vasoconstrictors and vasodilators modulates the vessel resistance (6). In the course of hypertension the homeostatic balance becomes perturbed, i.e. the influence of vasoconstrictors as AT II, endothelin-1, thromboxane A₂ etc., predominates over the vasodilation caused by NO. Moreover, other vasoactive substances are now recognized as factors able to modulate the critical cellular processes involved in vascular remodeling and lesion formation (6). Except of these effects on cellular vascularity, AT II may also mediate remodeling and lesion formation by altering of extracellular matrix composition and under the influence of other substances (6). Moreover, the migration of endothelial and smooth muscle cells can be modulated by AT II as well. Similar vasoconstrictive effects have been described in other substances like norepinephrine.

Role of NO

Endogenous vasodilator like NO or natriuretic peptides appear to have a countervailing influence to AT II. Vasodilators generally inhibit vascular smooth muscle cell growth. They also may promote a decrease in vascular smooth muscle cellularity by inducing the programmed death. Taken together, one may speculate, that decreased NO generation is associated with shrinkage remodeling, whereas increased NO generation is associated with enlargement remodeling. Similarly, an increase in oxidative stress will mitigate the vasodilatory bioactivity of NO. The imbalance between NO and reactive oxygen species, characterizing the endothelial dysfunction

development, may be an important pathogenic mechanism in hypertension, that determines the level of blood pressure, promotes alterations in vessel structure and contributes to hypertension complications such as CAD.

Role of ACE Inhibition : Perspectives in Prevention of Endothelial Dysfunction

To the degree that vascular disease is characterized by an imbalance between a relative increase in AT II and a relative deficit of NO bioactivity, it is postulated that ACE inhibition may effectively restore the appropriate homeostatic balance between these vasoactive systems. This hypothesis has been now tested in clinical trials (18,23). There is a compelling evidence indicating that long-term administration of ACE inhibitors reverses endothelial dysfunction in patients with either hypertension or atherosclerotic vascular disease. They appear to have particular efficacy in reversing vascular remodeling process and thus prevent from the eventual hypertension development as well as in patients with existing essential hypertension (23,30). This observation supports the hypothesis, that antihypertensive agents that reduce blood pressure and reverse the remodeling process may substantially change the natural history and the course of the disease. Beneficial effects of ACE inhibitors has been proven in patients with left ventricular dysfunction due to hypertrophy (2,18,21,23). They reduced the incidence of recurrent myocardial infarctions as well. This fact indicates, that ACE inhibitors may alter the natural history of CAD, possibly via direct effects on coronary vascular function and structure. It has been documented, that ACE inhibitors probably reduce the myocardial oxygen consumption in association with an increase in NO generation either. These findings are consistent with previous studies demonstrating that NO has a direct effect on muscle oxidative metabolism. It raise the possibility, that ACE inhibition may prevent myocardial ischemia by optimizing the balance between myocardial oxygen supply and demand. Furthermore, there are clinical studies under way that will directly test the hypothesis that chronic administration of ACE inhibitors in normotensive individuals with CAD will prevent ischemic events (3).

POTENTIAL INTERVENTIONS IN ENDOTHELIAL DYSFUNCTION

1) Nonpharmacological Interventions

With the knowledge of endothelium functions some interventions targeted exclusively at the endothelium monolayer may be developed in the future in order to improve endothelial dysfunction sequelae.

Low-cholesterol Diet

It has been found out, that dietary treatment restored impaired endothelium-dependent vascular relaxation (8). Particularly high intake of fish oil appeared to result in a low incidence of CAD. Fatty acids in marine fish oil differ chemically from those of land animals and vegetable oil – they contain greater percentage of polyunsaturated fatty acids, which are less vulnerable to oxidation. Eicosapentaenoic and docosahexaenoic acids in marine lipids can substitute to arachidonic acid. Like arachidonic acid, they can be converted into an active form of prostacyclin (a vasodilator and platelet aggregation inhibitor). Unlike arachidonic acid, they are converted into an inactive form of thromboxane A₂ (vasoconstrictor and platelet agonist). Therefore, these omega-3 fatty acids shift the balance in the arachidonic acid cascade to the side of the vasodilator/platelet antagonist prostacyclin.

Exercise

Beneficial effect of regular physical activity on endothelial dysfunction is now recognized due to increased endothelium-derived NO release via the shear stress effects.

Smoking cessation

The improvement in vascular function that follow cigarette smoking cessation particularly reverses the adverse effect of smoking on vasculature. Moreover, the lipid profile also benefits from smoking cessation due to HDL- cholesterol and apolipoprotein A-1 increase, whereas triglycerides decrease.

Antioxidant supplements

Because oxidation of LDL-cholesterol contributes to endothelial dysfunction, researchers have reasoned, that a diet rich in antioxidants may be protective, but results of clinical studies have not

consistently shown a benefit of administering substances like vitamins E, C, beta-carotene, minerals as selenium and coenzymes, e.g. Q10 or non-vitamin antioxidants as flavonoids.

L-arginine supplementation

With the recognition of NO function, interest has begun to center on L-arginine, the precursor of NO. It has been hypothesized, that increasing availability of L-arginine might enhance synthesis of NO and thereby promote vasodilation, but the evidence for that hypothesis has been still missing.

2) Pharmacological Interventions

There are several categories of drugs used to treat cardiovascular diseases that have proven its primary medical effect to ameliorate or even improve an impaired endothelial cells relaxing effect.

Lipid-lowering agents

Particularly s.c. statins, i.e. HMG-CoA reductase inhibitors, improve vasodilative response in a long-term treatment. The effect was significantly greater in combined therapy with antioxidant substances that have been added to the regimen (1,3).

ACE inhibitors

AT II as a potent endothelium-derived contracting factor is produced by the action of ACE from angiotensin I. It is normally balanced by the effects of NO and prostacyclin. When the endothelium is damaged or dysfunctional, however, the countervailing effects of these endothelial vasodilators are lessened. Improvement of endothelial dysfunction with antihypertensive agents, particularly those with long duration of action like trandolapril, ramipril, perindopril or quinapril as demonstrated in TREND Study(18), seems to be reasonable and thus applicable.

Calcium-channel blockers

Hypertension treatment with a new generation of dihydropyridine calcium antagonists e.g. amlodipin, has inhibited to a partial degree atherogenesis in humans, particularly development of new lesions. Unfortunately, there

has been not yet the evidence, that they modify existing ones (1).

Estrogen replacement

The beneficial effect of estrogens to enhance endothelial vasodilative function may be due to an antioxidant effect or to an estrogen-induced enhancement of NO synthase expression.

CLINICAL SEQUELAE OF ENDOTHELIAL DYSFUNCTION FOUND IN CZECH MILITARY CREWMEMBERS.

Based on what has been said so far, the main task should have been to preserve an intact or to improve an impaired endothelial integrity and function. It is more important from a preventive point of view, when we take into an account that endothelial dysfunction occurs prior to irreversible structural changes. Reasonable and appropriate therapy should have been initiated more earlier particularly in individuals with hypertension, familial hypercholesterolemia and hyperglycemia. Corrections or preventive countermeasures to influence the endothelial dysfunction with agents targeting the endothelium, should have been applied as soon as possible particularly in flying personnel at higher risk profile (3,29). It is the only way how to improve the clinical outcomes and prospects in these patients not only becoming older, but also threatened by above mentioned illnesses. Keeping this all in mind, we made an analysis among the group of 21 Czech military aviators, who were treated primarily for hypertension within the 5 years period (1994 – 1998).

DESIGN AND THE OUTCOMES OF THE STUDY

Aviators were sorted out in terms of age, rank, flying class, aircraft to be flown, other coexisting disorders, therapy strategies, onset and duration of medication. Special attention was paid to presence of other risk factors and bad life style habits, individual compliance and cooperation during crewmembers regular actions and follow-up. The mean age of involved aviators was 46 years (31 - 59). Two thirds were higher ranking officers, one third lower ranking ones. Mean duration of medication lasted 4,62 years (0,2 – 13). Only hypertension was found in 14,30%, another two

underlying diagnoses in 66,70% and in 19% more than two chronic illnesses were found. Two combination therapy strategy was used in 57,20%, monotherapy in 42,80% was administered. Within the study the therapy selection was changed in 53,40%. We stopped using nonselective betablockers and dihydropyridine Ca antagonists like nifedipin at all. We substituted them with betaxolol and calcium channel blockers with longer duration of action as verapamil and amlodipin and ACE inhibitors like trandolapril and ramipril respectively. Diuretics have remained in the treatment of hypertension as a "golden standard". Furthermore, 4 crewmembers were treated for hypercholesterolemia with lovastatin, pravastatin and fenofibrates, 2 with allopurinol because of hyperuricemia. We did not observe any unwanted side effects during the therapy. When searching for the presence of other risk factors, we found out cigarettes smoking in 23,80%, hyperlipidemia in 81,00%, hyperuricemia in 38,10% and overweight in 85,70% (BMI>25). Positive medical history for CAD was found in 47,10%. We succeeded in good control of hypertension pharmacologically, but we failed in influencing and elimination of present risk factors and bad life style habits. No wonder, that within the 5 years period 3 cases of myocardial infarction occurred. It should be stressed, that all 3 aviators had hyperlipidemia, two of them were recent stop-smokers, one was treated for peripheral vessel disease of atherosclerotic origin in the past 4 years. Until the CAD event, they were treated with propranolol and nifedipin.

DISCUSSION AND AEROMEDICAL CONSIDERATIONS

Coronary artery disease, which continues to be a leading cause of morbidity and mortality, is one presentation in a continuum of events that may lead to its end-stage, i.e. clinical manifestation with its sequelae from an aeromedical point of view as documented by many studies (3,14,20,24,26,29). Common to the pathogenesis of most cardiovascular diseases are the conditions often called risk factors. That cause pathologic changes and dysfunction both in the heart and blood vessels, and lead to function impairment more earlier prior to clinical manifestation (23). In the last decade, our understanding of the pathogenesis of cardiovascular diseases has increased. One important result of this is recognition of the central role played in

circulatory homeostasis by the cells that line the vascular system – the endothelium. Endothelium, generally considered, have many critically important functions. These include synthesis and release of biologically active substances that have either local and distant functions within the blood vessel wall or at its surface. The pathophysiological changes that occur in endothelial cell structure and function also characterize many of the pathomechanisms responsible for development and progression of atherosclerosis and CAD. We currently know, that many of s.c. risk factors for CAD can be modified by non-pharmacological or pharmacological interventions. As shown above, endothelial dysfunction lies „ at the heart „ of a wide spectrum of cardiovascular diseases. In contrast, as it has been shown in our group of hypertensive airmen, those who ended-up their professional career due to CAD development were treated mostly with remedies having efficient effect only on blood pressure level, but hardly ever beneficial effect on endothelial function. Similarly individuals with hyperlipidemias, despite the treatment with statins, were subjected probably to an inappropriate regimens and an ineffective pharmacological control of known metabolic disorders. Other changeable risk factors like smoking and lack of physical activity are both long-lasting aeromedical problems we have been facing with for a long time. In fact, it still remains a common challenge not only for commanders, flight surgeons, but especially for aviators - to change such an undesirable trend. There is a need to change their own minds i.e. to be more involved in personal attitude toward the sound life style in order to be fit to flying. Higher intake of fish oils is another sophisticated approach how to contribute to endothelium cells protection as well as to reduction in higher consumption of sugary food preventing from deteriorating oxidant stress sequelae. On the other hand the supplementation with estrogens, L-arginin, seems to be reasonable but questionable because of the safe administration. Further clinical trials will be needed to prove their beneficial effects in prevention of endothelial dysfunction development. Moreover, it should be taken into an account expected problems with the waiverability of these substances. When we turn back to the question at the headline, we can state, that aging or process of aging has been grasped more or less as a biological term. It is now clear, that the process of aging encompasses many

simultaneously undergoing changes on cellular and biochemical level, characterized by a decrease of relaxing substances and an increase of contracting ones, resulting in their dysbalance. Involved in that process are enzymes, hormones, metabolic products, toxins, mechanical stress, nutritious factors, endocrine substances, exogenous factors, stress, as well as an emotional profile. With the presence of particular s. c. risk factors as stated, the result is endothelial dysfunction as an initial stage, later on the end-organ damages occur, obviously earlier then expected with a deleterious impact on the health status. These facts are now more understandable and this knowledge gives us more chances to slow down conditions indisputably linked with aging. This is our professional mission to move on and try to shift forward the care our aviators deserve.

CONCLUSIONS

Based on what has been expressed so far, we can formulate possible pathways in order to reverse undesirable impacts of aging particularly on cardiovascular system. The reason is clear -- cardiovascular diseases represent still the most frequent reason for disqualification from flying status.

Changeable factors:

Hypertension

When selecting a convenient remedy, it should be preferred the use of ACE inhibitors and Calcium channel blockers with long and ultra-long duration of action as the first step therapy if not contraindicated

Hyperlipidemias

The reasonable lipid-lowering agents, besides the strict dietary regimens, should be mainly statins administered, followed by a regular specialist supervision

Smoking

To resolve that problem requires to start with programmes like preference of non-smokers among the candidates or enhance educational programmes among smokers in order to persuade them about the advantage of quitting smoking particularly for health status and career prolongation.

Sedentary life style

Sufficient and regular physical activity should be a part of flight training during the whole career along with the weight control.

Higher intake of sugary food and alcohol

Restriction of both has a proven beneficial effect in preventing from endothelial dysfunction development via inhibition of vascular endothelial growth factor effects and ameliorates oxidative stress sequelae not only for the endothelial cells as well.

Unchangeable factors

Advancing age
Positive medical history for C-V diseases

Unresolved factors

Hyperuricemia
Hyperinsulinemia
L-arginin, estrogen administration
Behavioral type
Hyperdynamic circulation
Stress

Disclaimer: The opinions and recommendations contained herein are the personal views of the author and are not to be construed as reflecting the views of Czech Air Force and Ministry of Defense. Moreover, the author offer this essentially as a discussion paper to sound out the views of interested and informed colleagues rather than as a finished viewpoint.

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